REMARKS/ARGUMENTS

Applicants respectfully request reconsideration and allowance of this application in view of the amendments above and the following comments.

Restriction Requirement

According to the Examiner, "[a]lthough the election [in the reply filed on June 30, 2008] is made with traverse, Applicants have not presented any reasoning to support the traversal." Applicants respectfully disagree.

In the reply of June 30, 2008, Applicants specifically argued:

1) The Examiner should not require any restriction pursuant to List II as List II was compiled from dependent claims 12-14 and unity of invention has to be considered in the first place only with reference to the independent claims. See the second and third paragraphs on page 3 of that reply.

2) The Examiner should not require restriction between connexins and innexins because they are functionally similar alternatives and, therefore, properly claimed and examined together. See the first sentence of the fourth paragraph on page 3 of that reply.

3) Although the Examiner alleged that connexins and innexins do not form a single inventive concept in that they lack the same special technical features, the Examiner did not indicate what the Examiner considered to be the special

technical feature of either species that was not shared by the other. See the remainder of the fourth paragraph on page 3 of that reply.

4) Under the procedures set forth in MPEP § 1850(III)(B), providing for Markush practice under the PCT, the special technical features defined in PCT Rule 13.2 shall be considered to be met when the alternatives are of a similar nature and, according to (B)(2), "belong to a recognized class of chemical compounds in the art to which the invention belongs." See the paragraph bridging pages 3-4 of that reply.

5) As discussed in the instant specification at page 5, lines 18-27; and page 7, lines 12-15, connexins and innexins belong to a recognized class of cell communication proteins and, therefore, are sufficiently similar in nature that restriction therebetween is not proper under PCT Rule 13.2. See the first and second full paragraphs on page 4 of that reply.

Respectfully, Applicants have provided numerous arguments in support of the traversal and it is unclear why the Examiner says they have made no arguments in support of the traversal. To the extent that the Examiner is ignoring these arguments, Applicants respectfully submit that this is improper. Applicants respectfully request that the Examiner provide a proper response to such arguments or, preferably, reconsider and withdraw the restriction requirement.

Information Disclosure Statements

The "missing" references AC (Hodgkin et al.), AT (Brewer, G.J.), AV (Allen, J.R.C.), AG (Oh et al.), AH (Yamamoto et al.) and AI (Postma et al.) have all now been supplied. Applicants respectfully request that the Examiner now consider these documents.

With respect to AD (Hodgkin et al.), there appears to be no such citation. Applicants have provided two alternative citations (2 and 3 on the information disclosure statement filed February 2, 2009), either of which may be the originally intended document. If the Examiner wishes Applicants to amend the specification either to delete the original reference or to correct the original reference to one or both of the alternative citations, Applicants respectfully request a statement to that effect in the next Office Action or, hopefully, the Notice of Allowability.

Substantive Issues

The specification was objected to because there was no Brief Description of the Drawings. In response, Applicants have amended the specification above to provide the missing header.

Claim 16 was objected to because of a certain informality, specifically reciting "at least one of" and simultaneously "and/or." In response, Applicants have amended claim 16 to recite customary Markush language, i.e., "a member selected from the group consisting of X, Y and Z."

Claims 11, 12 and 15-17 were rejected under 35 USC § 103(a) as being obvious over Mazet et al. ("Mazet"), *Eur. J. Biochem, 210:* 249-256 (1992), in view of Barbier et al. ("Barbier"), US 2004/0126817. In response, Applicants respectfully submit that the combination of Mazet and Barbier does not make out a *prima facie* case of the obviousness of the rejected claims. Therefore, Applicants respectfully request that the Examiner reconsider and withdraw this rejection.

Main claim 11 is directed to a measuring arrangement for measuring an electrical signal on biological membrane bodies, whereby an electroconductive access into the membrane body is created by gap junction channels (see also abstract of the present application).

According to paragraph [0025] of the specification, published as US 2005/0027139, the object of the present invention is to develop improved methods for carrying out electrochemical studies on membrane bodies.

According to paragraph [0039], "membrane bodies" in the context of the invention are volume elements filled with a liquid and enclosed by a membrane; membrane bodies according to the invention are preferably biological membrane bodies, e.g. living cells.

According to paragraph [0026], the electrical measurements allow conclusions to be drawn about the state and the behavior of membrane-integrated biomolecules, and about their reaction to prospective effector molecules.

According to claim 11 the measuring arrangement for measuring an electrical signal on a membrane body, comprises:

a) an electrical measuring instrument;

b) electrodes;

c) a membrane comprising at least one connexin or innexin; and

d) a membrane body comprising at least one connexin or innexin;

wherein the connexins and/or innexins in the membrane and membrane body cooperate to form at least one gap junction channel, and an electrically conducting access is produced from a side of the membrane facing away from the membrane body to an interior of the membrane body by said at least one gap junction.

Thus, gap junctions between a membrane and a membrane body are used to produce an electrically conducting access to an interior of the membrane body in order to gain insight into the behavior of membrane-integrated biomolecules.

Mazet deals with the characterization of gap junctions per se. To quote Mazet (page 210, left column): "*The question is how to correlate the activity of the channel to its structure. In the present report, we have focused on voltage-dependent gating properties.*" So, Mazet's objective is totally different from the objective of the present invention. Applicants respectfully submit that a person having ordinary skill in the art would not have consulted Mazet in order to find improved methods for carrying out electrochemical studies on membrane bodies, particularly since Mazet does not deal with membrane bodies in at all.

Furthermore, Mazet did not disclose a measuring arrangement for measuring an electrical signal on a membrane body, as required by the present claims. Mazet disclosed a measuring arrangement for measuring an electrical signal on a membrane. More specifically, Mazet describes a planar bilayer that is initially devoid of connexins or gap junctions. In a second stage, a proteoliposome preparation containing connexin is incorporated into the planar bilayer, thus producing a bilayer that does contain connexin. Subsequently, Mazet studies the electrical properties, specifically the conductance and the voltage dependence, of the bilayer and of the

connexins incorporated therein. There is no teaching or suggestion in Mazet to measure an electrical signal on a membrane body.

The measuring arrangement required by instant claim 11 is much more complex than the measuring configuration disclosed by Mazet. Besides a membrane, the measuring arrangement according to claim 11 contains a membrane body comprising at least one connexin or innexin. Furthermore, the connexins and/or innexins in the membrane and membrane body cooperate to form at least one gap junction channel, and an electrically conducting access is produced from a side of the membrane facing away from the membrane body to an interior of the membrane body by said at least one gap junction.

Mazet does not teach or suggest using the bilayer therein with its incorporated connexins as a substrate for more complex configurations, or for a purpose other than to study the properties of the connexons or gap junctions themselves.

Further, Mazet would not have motivated persons skilled in the art to enhance Mazet's measuring configuration in order to study membrane bodies instead of gap junctions.

In fact it is highly questionable, as will be explained in greater detail below, whether the bilayer disclosed by Mazet could be used for studying membrane bodies at all.

Barbier does not heal the above-noted deficiencies of Mazet. Consequently, the combination of Mazet and Barbier fails to make out a *prima facie* case of the obviousness of any of the rejected claims.

Barbier describes an assay involving two types of cells, both containing connexins, and a biochemical signal transfer through the gap junctions. Barbier's concept differs from the present invention in several decisive aspects:

(1) Barbier discusses only gap junctions formed between two cells; nowhere does Barbier suggest that one side of the gap junction may be formed from a lipid bilayer other than a living cell membrane.

(2) Barbier restricts itself entirely to biochemical or optical detection methods, for the simple reason that the method described therein does not allow any direct electrical measurement from the paired cells.

(3) Barbier employs the measuring configuration described therein solely for the purpose of investigating the gap junction proteins themselves, for example; to detect ligands that alter the properties of the gap junctions; nowhere does Barbier teach or suggest the use of gap junctions as a tool to investigate the properties of membrane bodies.

Thus, a person having ordinary skill in the art would not have considered Barbier in finding a solution to the technical problem sought to be solved with the arrangement provided by claim 11: development of improved methods for carrying out electrochemical studies on membrane bodies. Instead, Barbier clearly deals with, and, therefore, would have been considered to be limited to "a gap junction assay method and methods for both characterizing connexins and for identifying compounds that affect gap junctions function."

However, even assuming, merely for the sake of argument, that a person having ordinary skill in the art would have considered Barbier, such a person would not have found any teaching

or suggestion for improved electrochemical studies on membrane bodies, since Barbier does not mention electrochemical studies on membrane bodies at all.

Moreover, a person having ordinary skill in the art would not have been motivated to combine the disclosures of Mazet and Barbier in the first place since Mazet deals with electrical measurements and Barbier deals with optical measurements.

And even if one ordinary skill in the art did combine the disclosures of Barbier and Mazet, such a person would never have achieved the subject matter of claim 11 or any of the other rejected claims, as both references deal with characterization of gap junctions and not with the characterization of membrane bodies by using gap junctions.

Certainly, persons skilled in the art would have had no reasonable expectation of success in the proposed combination, even if, assuming for the sake of argument, there was some teaching or suggestion or other evidence of motivation to carry it out. It is not true, as the Examiner apparently implies, that it would have been expected to be a simple, straight-forward modification to place a cell in contact with Mazet's lipid bilayer. Quite the contrary, a reasonable expectation of success was entirely lacking. A free standing lipid bilayer, as described by Mazet, is by nature a fragile and instable structure (like a soap bubble), and a person having ordinary skill in the art would have been reasonable to have expected that, if a cell is placed on or near it, the bilayer would deform or rupture long before any connexins found each other and interacted to form a stable gap junction (like a soap bubble usually bursts when it lands

on the ground). Indeed, this is why the present application proposes to use a mechanically more stable, suspended or supported bilayer as a substrate for the measuring configuration.

In view of the foregoing, Applicants respectfully submit that the combination of Mazet and Barbier does not make out a *prima facie* case of the obviousness of any of the rejected claims. Therefore, Applicants respectfully request that the Examiner reconsider and withdraw this rejection. An early notice that this rejection has been reconsidered and withdrawn is earnestly solicited.

Claim 13 was rejected under 35 USC § 103(a) as being obvious over Mazet in view of Barbier and further in view of Xu et al. ("Xu"), US 5,874,668. In response, Applicants respectfully point out that this rejection was dependent upon the combination of Mazet and Barbier making out a *prima facie* case of the obviousness of the basic aspects of the present invention, which, Applicants have explained above is not, in fact, the case. There is nothing in the combination of Mazet and Barbier with Xu that overcomes the deficiencies in the combination of Mazet and Barbier. Indeed, Xu is relied upon to teach a reconstituted membrane at the end of a patch clamp electrode. Xu does not remedy the fact, as indicated previously, that Mazet and Barbier are not properly combinable; that Mazet and Barbier deal with different types of measurements, one electrical and one optical, and, therefore, even if combined would not achieve the present arrangement; or that the combination of Mazet and Barbier fails to reveal a reasonable expectation of success in coupling a membrane body to Mazet's membrane.

Consequently, Applicants respectfully submit that the combination of Mazet, Barbier and Xu also fails to make out a *prima facie* case of the obviousness of claim 13.

Applicants further submit that Xu is completely irrelevant to the instant subject matter. While it is true that Xu forms a lipid bilayer on the tip of a patch pipette, this in itself is definitely very early prior art, having been described in the 1980's by numerous authors. Moreover, Xu employs this configuration only to provide certain membrane proteins (including, for the purpose of illustration, a connexin) in a bilayer for the purpose of atomic force microscopy, which is a completely different method and pursues completely different goals from the electrical assays described in the present application.

In view of the foregoing, Applicants respectfully submit that the Examiner would be fully justified to reconsider and withdraw this rejection as well. An early notice that this rejection has also been reconsidered and withdrawn is earnestly solicited.

Applicants believe that the foregoing constitutes a bona fide response to all outstanding objections and rejections.

Applicants also believe that this application is in condition for immediate allowance. However, should any issue(s) of a minor nature remain, the Examiner is respectfully requested to telephone the undersigned at telephone number (212) 808-0700 so that the issue(s) might be promptly resolved.

Early and favorable action is earnestly solicited.

Respectfully submitted,

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